

REMARKS

Claims 8-15 and 80-83 are pending in the instant specification. Applicants have amended claims 8, 10 and 13. Support for the amendment to claim 10 can be found, for example, on page 50, lines 12-15 of the instant specification. Support for the amendment to claim 13 can be found, for example, on page 45, line 30 of the instant specification. Applicants have added claims 80-83. Support for claims 80-83 can be found, for example, in claim 8 as filed. Applicants have amended the specification to make the title more descriptive. No new matter is added.

Claim Objections

The Examiner objected to claims 8-15, on page 2 of the Office Action, for referring to non-elected subject matter. Applicants have amended claim 8 to delete reference to non-elected subject matter. Accordingly, Applicants respectfully request that this objection be withdrawn.

Specification

The Examiner objected to the title as not being descriptive. Applicants have amended the title, as the Examiner suggested. Thus, Applicants request that this objection be withdrawn.

Priority

The Examiner asserted, on pages 2-3 of the Office Action, that the present claims are entitled to the priority of U.S.S.N. 09/578,534, filed May 24, 2000 and not to U.S.S.N. 09/431,352, U.S.S.N. 09/320,395 or U.S.S.N. 08/813,456. The Examiner argued that the latter three applications did not teach kits for determining the existence of susceptibility to developing restenosis in a subject wherein said kit comprises a primer that hybridizes to the 5' or 3' of IL-1RN (VNTR) allele 1. Applicants respectfully traverse.

Applicants submit that U.S.S.N. 09/431,352, U.S.S.N. 09/320,395 and U.S.S.N. 08/813,456 all teach kits comprising a primer that hybridizes to the 5' or 3' of IL-1RN (VNTR) allele 1. U.S.S.N. 09/431,352 teaches such kits from page 13, last paragraph to page 14, last full paragraph, and from page 81 to the end of the "Genotyping IL-1RN" section on page 82. U.S.S.N. 09/320,395 teaches such kits from page 7, first full paragraph, to page 8 first full paragraph and the "Genotyping IL-1RN" section on page 53. U.S.S.N. 08/813,456 (issued as U.S. Patent No. 6,210,877) teaches such kits from column 6, line 51 to column 7, line 15 and

from column 7, line 66 to column 8, line 30. Further, as explained below, U.S.S.N. 08/813,456 (issued as U.S. Patent No. 6,210,877) was used in an anticipation rejection of claims 8-15, further demonstrating by the Examiner's admission, that this application must support a proper priority claim to claims 8-15 of the instant application.

In all of the above cited sections, these applications teach a kit for the detection of an allele. In the "Examples" section of each of the applications methods for detecting any of alleles 1-5 of the IL-1RN VNTR are described. Thus, all of the above applications teach kits comprising a primer that hybridizes to the 5' or 3' of IL-1RN (VNTR) allele 1. Applicants submit that all claims are entitled to an earliest priority date of March 10, 1997, the filing date of U.S.S.N. 08/813,456.

Claim Rejections

35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 10 and 13, on pages 3-4 of the Office Action, under 35 U.S.C. §112, second paragraph, for indefiniteness. The Examiner asserted that claim 10 was indefinite for reciting "said first primer and said second primer hybridize to a region in the range between about 50 and 1000 base pairs". The Examiner also asserted that claim 13 was indefinite for reciting a list of detection methods when the claim introduced a list of detection means.

Applicants have amended claim 10 to replace "hybridize to a region in the range between about 50 and 1000 base pairs" with "hybridize between 25 and 2500 base pairs apart". Also, Applicants have amended claim 13 to replace "detection means" to recite "the kit is used to perform a detection method". In light of these amendments, Applicants submit that claims 10 and 13 are definite and request that this rejection be withdrawn.

35 U.S.C. §112, First Paragraph

Written Description

The Examiner has rejected claims 8-15, on pages 4-8 of the Office Action, under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner alleged that there was no written description for primers which hybridize to IL-IRN VNTR allele 1 or alleles in linkage disequilibrium with IL-IRN VNTR. Applicants respectfully disagree in light of the amendments to the claims made, herein.

Applicants submit that there is sufficient written description for primers which hybridize to IL-IRN VNTR allele 1. The Examiner argued on pages 7-8 of the Office Action as follows:

Adequate written description requires more than a mere statement that nucleic acids are part of the invention and reference to a potential method of identification. The particular nucleic acids are required. (Emphasis added).

Applicants submit that the particular nucleic acids claimed are not necessary to satisfy the written description requirement. The "Guidelines for the Examination of Patent Applications under 35 U.S.C. 112 paragraph 1 'Written Description' Requirement," Federal Register, Vol 66, No. 4, pages 1099-1111, Friday January 5, 2001, cited by the Examiner on page 8 of the Office Action, states on page 1101:

Describing the complete chemical structure, *i.e.*, the DNA sequence, of a claimed DNA is one method of satisfying the written description requirement, but it is not the only method. *See* Eli Lilly, 119 F.3d at 1566, 43 USPQ2d at 1404 ("An adequate written description of a DNA * * * requires a precise definition, such as by structure, formula, chemical name, or physical properties." (emphasis added, internal quote omitted)). Therefore, there is no basis for a per se rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequence disclosed.

Applicants have provided enough information for one having ordinary skill in the art to make and use the primer sequences of claim 8 based on the physical properties of these primers, *i.e.* their ability to make an amplification product that may be used to detect the IL-IRN VNTR alleles, based on the state of the art at the time of the earliest priority date of the instant application. Applicants have provided the sequence of IL-IRN and the different amplification product sizes of various IL-IRN VNTR alleles when nucleic acid molecules corresponding with SEQ ID NOs:7 and 8 are used as PCR primers.¹ Further, the positions where SEQ ID NOs:7 and

¹ See Figure 3 and page 87, lines 1-10 of the instant specification.

8 hybridize to IL-1RN are shown.² At the time of the earliest priority date of this application, March 10, 1997, the use of polymerase chain reaction (PCR) and methods for determining appropriate primer sequences for PCR were well known to those having ordinary skill in the art. This is evidenced by references published before the earliest priority date of the instant application³, filed herewith.

Many papers were published on methods of selecting primers and other conditions for amplification of selected nucleic acid sequences. These references include Breslauer, K. J., *et al.* (1986) Proc. Natl. Acad. Sci. USA 83, 3746-3750 ("Exhibit A"); Rychlik, W. and Rhoads, R. E. (1989) Nucleic Acids Res. 17, 8543-8551 ("Exhibit B"); and Rychlik, W., *et al.* (1990) Nucleic Acids Res. 18, 6409-6412 ("Exhibit C"). Copies of these references are provided herewith.

Exhibit A teaches the production of the complete thermodynamic library of all 10 Watson-Crick DNA nearest-neighbor interactions.⁴ Exhibit A further teaches that armed with this knowledge, "scientists will be able to predict the stability (ΔG°) and the melting behavior (ΔH°) of any DNA duplex structure from inspection of the primary sequence."⁵ Thus, the optimal conditions for hybridization can be determined and primers designed for any given DNA sequence including the sequences 5' and 3 of IL-1RN VNTR allele 1, IL-1A (+4845) allele 1, IL-1B (-511) allele 1, IL-1B (+3954) allele 1, and IL-1RN (+2018) allele 1. Thus, one of ordinary skill in the art would have been able to determine what primers could be used to detect any of the above-recited alleles.

Further, Exhibit B, teaches factors that are important for the design of PCR primers⁶ and a computer program (OLIGO) for the prediction of what primers would be effective.⁷ Exhibit C teaches methods of optimizing the annealing temperature for primers designed using the OLIGO

² *Id.* at page 87, lines 1-10.

³ Manuals teaching the selection PCR primers published prior to the earliest priority date of the instant application include: Dieffenbach, C. W. and Dyeckler, G. S. (1995) PCR Primer A Laboratory Manual. Cold Spring Harbor Laboratory Press. Cold spring Harbor, NY.; Innis, M. A., Gelfand, D. H., Sninsky, J. J., and White, T. J., eds. (1990) PCR Protocols A Guide to Methods and Applications. Academic Press. San Diego, CA; Rychlik, W. (1993) Selection of primers for polymerase chain reaction, in Methods of Applications (White, B. A., ed.) Humana, Totowa, NJ, pp. 31-40. Further, many references published before the earliest priority date of the instant application teach how to select PCR primers for a give nucleic acid sequence, including: Breslauer, *et al.* Proc. Natl. Acad. Sci. USA 83, 3746-3750 (Exhibit A); Rychlik, W. and Rhoads, R. E. (1989) Nucleic Acids Res. 17, 8543-8551 (Exhibit B); and Rychlik, *et al.* (1990) Nucleic Acids Res. 18, 6409-6412 (Exhibit C). These references are discussed further in the Declaration under 37 CFR § 1.132 by Kenneth Komman, filed herewith.

⁴ See Exhibit A at the Abstract.

⁵ *Id.*

⁶ See Exhibit B at the last full paragraph on page 8543.

⁷ *Id.* at 8544.

program to optimize the yield of the specific amplification product of the PCR reaction. Thus, tools had been established by the time of the earliest priority date of the instant application to allow those having ordinary skill in the art to not only select and/or design primers for just about any given DNA sequence, but to optimize the amount of specific product produced by these primers. I submit that there is enough disclosure in the instant application, *i.e.* the sequence to be amplified, to allow one of ordinary skill in the art to produce any number of primers to detect any of IL-1RN VNTR allele 1, IL-1A (+4845) allele 1, IL-1B (-511) allele 1, IL-1B (+3954) allele 1, or IL-1RN (+2018) allele 1.

Thus, the present disclosure provides sufficient guidance such that one of ordinary skill in the art would have been able to make primers that hybridize to IL-1RN VNTR allele 1. The same is true for primers that hybridize to IL-1RN (+2018).

Moreover, Applicants submit that the claims as amended no longer encompass any allele in linkage disequilibrium with IL-1RN (VNTR). Applicants have amended claim 8 to delete language referencing linkage disequilibrium.

For the above reasons, Applicants submit that claims 8-15 meet the written description requirement and request that this rejection be withdrawn.

Enablement

The Examiner has rejected claims 8-15, on pages 8-19 of the Office Action, under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner argued that the specification is not enabled for a kit that predicts a subjects' predisposition for restenosis. Applicants have amended claim 8 from which claims 9-15 depend. Applicants submit that the claims as currently pending are enabled and request that this rejection be withdrawn.

35 U.S.C. §102

The Examiner has rejected claims 8-10 and 12-15, on page 20 of the Office Action, under 35 U.S.C. § 102(b) for being anticipated by GIBCO BRL Catalog (1995/1996; pages 18-15 and 18-16 (“GIBCO”). The Examiner alleged that GIBCO teaches a kit for labeling DNA comprising a random primer solution which hybridizes to the IL-1A (+4845) allele and alleles in linkage disequilibrium with IL-1A (+4845) allele 2, biotin-14-dCTP, dNTPs, DNA polymerase and control DNA. Applicants respectfully traverse this rejection in light of the amendments made to the claims herein.

Applicants have amended claim 8 to delete reference to alleles in linkage disequilibrium with IL-1RN VNTR. GIBCO does not teach a kit comprising primer oligonucleotides that hybridizes 5' or 3' to IL-1RN VNTR allele 1 as encompassed by claim 8 as presently amended. GIBCO fails to teach each and every element of the present claims and therefore, cannot anticipate claim 8 or its dependent claims 9-15. Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on pages 20-21 of the Office Action, under 35 U.S.C. § 102(b) for being anticipated by Cominelli *et al.* WO 97/25445 (“Cominelli”). The Examiner alleged that Cominelli teaches a kit for detecting IL-1RN allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that Cominelli was published on July 17, 1997. The earliest priority date of the instant application is March 10, 1997. Thus, Cominelli cannot be 102(b) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on pages 21-23 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Duff *et al.* U.S. Publication No. 20050064453 (“Duff”). The Examiner alleged that Duff teaches a kit for detecting IL-1RN allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that Duff has an earliest priority date of June 30, 1999. The earliest priority date of the instant application is March 10, 1997. Thus, Duff cannot be 102(e) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on pages 23-24 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Duff *et al.* U.S. Patent No. 6,268,142 (“the ‘142 patent”). The Examiner alleged that the ‘142 patent teaches a kit for detecting IL-1RN allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that the ‘142 patent has an earliest priority date of May 29, 1997. The earliest priority date of the instant application is March 10, 1997. Thus, the ‘142 patent cannot be 102(e) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on page 24 of the Office Action, under 35 U.S.C. § 102(b) for being anticipated by Duff *et al.* U.S. Patent No. 5,698,399 (“the ‘399 patent”). The Examiner alleged that the ‘399 patent teaches a kit for detecting IL-1RN allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that the ‘399 patent published when it issued on December 16, 1997. The earliest priority date of the instant application is March 10, 1997. Thus, the ‘399 patent cannot be 102(b) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on page 25 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Duff *et al.* U.S. Patent No. 6,713,253 (“the ‘253 patent”). The Examiner alleged that the ‘253 patent teaches a kit for detecting IL-1RN allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that the ‘253 patent has an earliest priority date of October 10, 1996. However, this earliest priority date may not be used as a 102(e) date because it is the filing date

of a foreign application claimed under 35 U.S.C. § 119(a)-(d) and (f).⁸ The 102(e) date for the '253 patent is the date of the corresponding PCT application, October 9, 1997. The earliest priority date of the instant application is March 10, 1997. Thus, the '253 patent cannot be 102(e) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on pages 25-26 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Duff *et al.* U.S. Patent No. 6,210,877 ("the '877 patent"). The Examiner alleged that the '877 patent teaches a kit for detecting IL-1RN allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that the '877 patent is based on U.S.S.N. 08/813,456, the parent application that the Examiner alleged was not able to be used for a proper priority claim. Applicants submit that U.S.S.N. 08/813,456 has a proper claim of priority and may not be used in an anticipation rejection. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on pages 26-27 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Francis *et al.* U.S. Publication No. 20060252055 ("Francis"). The Examiner alleged that Francis teaches a kit for detecting IL-1RN allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that Francis has an earliest priority date of March 10, 1997. The earliest priority date of the instant application is also March 10, 1997. Thus, Francis cannot be 102(e) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on pages 27-29 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Duff *et al.* U.S. Patent No. 6,706,478 ("the '478 patent"). The Examiner alleged that the '478 patent teaches a kit for detecting IL-1RN VNTR

⁸ See MPEP 2136.03.

allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that the earliest priority date of the '478 patent is May 29, 1997. The earliest priority date of the instant application is March 10, 1997. Thus, the '478 patent cannot be 102(e) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner has also rejected claims 8-15, on pages 29-30 of the Office Action, under 35 U.S.C. § 102(e) for being anticipated by Duff *et al.* U.S. Publication No. 20040152124 ("the '124 publication"). The Examiner alleged that the '124 publication teaches a kit for detecting IL-1RN VNTR allele 1 comprising primers, probes, reagents for an amplification reaction and a positive or negative control. Applicants respectfully traverse this rejection.

Applicants point out that the earliest priority date of the '124 publication is May 29, 1997. The earliest priority date of the instant application is March 10, 1997. Thus, the '124 publication cannot be 102(e) art to claims 8-15. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Double Patenting

The Examiner has rejected claims 8-15, on pages 30-31 of the Office Action, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7 of the '142 patent. Applicants submit, herewith, a terminal disclaimer disclaiming patent term which extends beyond the term of the '142 patent. Applicants submit that the terminal disclaimer renders this rejection moot.

The Examiner has rejected claims 8-15, on pages 31-32 of the Office Action, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-13 of U.S. Patent No. 6,746,839 ("the '839 patent"). Applicants submit, herewith, a terminal disclaimer disclaiming patent term which extends beyond the term of the '839 patent. Applicants submit that the terminal disclaimer renders this rejection moot.

The Examiner has provisionally rejected claims 8-10 and 12-15, on page 33 of the Office Action, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-20 of U.S. Patent No. U.S.S.N. 10/914,396. Applicants acknowledge the provisional rejection and will respond to it when allowable claims are found in either case.

CONCLUSION

A favorable action on the merits is respectfully requested. If further discussion of this case is deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below, and is assured of full cooperation in progressing the instant claims to allowance.

Respectfully submitted,

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